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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

April 30, 1999

Daniel R. Dwyer
Kleinfeld, Kaplan and Becker
1140 Nineteenth Street, N.W.
Washington, DC 20036-6601

Re: Food Master File 000625

Dear Mr. Dwyer:

The Food and Drug Administration (FDA) is responding to the submission, dated January 11, 1999, that you made on behalf of Lipton. FDA received this submission on January 12, 1999, and designated it as Food Master File 000625.

The subject of Lipton's submission is vegetable oil sterol esters. The submission informs FDA of Lipton's view that vegetable oil sterol esters are generally recognized as safe (GRAS) for use in vegetable oil spreads at levels up to 20% to supplement the nutritive value of the spread, and to help structure the fat phase and reduce the fat and water content of the spread. According to Lipton, the use of vegetable oil sterol esters in vegetable oil-based spreads is intended to help maintain healthy cholesterol levels as part of a diet low in saturated fat and cholesterol. The basis for Lipton's view that this use of vegetable oil sterol esters is GRAS is scientific procedures (21 CFR 170.30(b)). The submission includes the findings of a panel (Lipton's GRAS panel) of individuals who evaluated the data and information that are the basis for Lipton's GRAS determination. Lipton considers the members of its GRAS panel to be qualified by scientific training and experience to evaluate the safety of substances added to food.

According to Lipton, β-sitosterol, campesterol, and stigmasterol are the main sterol components of vegetable oil sterol esters. These sterols, which are obtained from vegetable oil distillates, are re-esterified with sunflower oil-derived fatty acids to improve their solubility. Lipton's submission describes the manufacturing process for vegetable oil sterol esters and proposes food grade specifications. Based on the use of vegetable oil sterol esters in vegetable oil spreads at levels up to 20%, Lipton estimates that consumer exposure to vegetable oil sterol esters would be approximately 1800 to 4800 mg/person/day. This intake of sterol esters corresponds to an estimated dietary intake of the sterol components of approximately 1100 to 3400 mg/person/day (i.e., approximately 18 to 57 mg/kg bw/day for a 60 kg adult). Lipton also estimates that this consumption from the use of vegetable oil sterol esters would result in a 4- to 14-fold increase in consumption of these substances relative to their current intake from other food sources.

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Lipton describes published and unpublished absorption, distribution, metabolism, and excretion studies in animals and humans. Based on these studies, Lipton concludes that vegetable oil sterol esters are hydrolyzed to free sterols in the gastrointestinal tract. Lipton also concludes that absorption of free sterols ranges from approximately 4 to 10 per cent in animals and humans, depending on the sterol, and that the phytosterols that are absorbed are rapidly eliminated from the body.

Lipton describes published and unpublished human studies that were conducted in support of the safety and efficacy of phytosterols in reducing serum cholesterol levels. Lipton's GRAS panel concluded that these human studies conducted with free phytosterols are pertinent to the evaluation of vegetable oil sterol esters because vegetable oil sterol esters are hydrolyzed in the gastrointestinal tract to free phytosterols and fatty acids. The data described in some of the published studies supported the approval of the drug *Cytellin*, which was marketed for many years. The sterol composition of *Cytellin* was 80 - 90 per cent β-sitosterol and therapeutic levels ranged from 9,000 to 30,000 mg of β-sitosterol per day.

The minimal absorption of vegetable oil sterol esters, coupled with their lipophilic nature, raises the question of the potential effect of vegetable oil sterol esters on the uptake of fat-soluble vitamins (Vitamins A, D, E, and K). Lipton addresses this potential effect in two ways. First, Lipton describes a published human study that includes a measurement of serum levels of Vitamins D, E, and K after 3.5 weeks of daily intake. This measurement showed some decrease in serum levels of Vitamin K at the highest concentration tested (i.e., 3.2 g free sterols/day). Second, Lipton analyzes published information about Vitamin K, including its high lipophilicity, its rapid half-life in serum, its low level of storage in the body (and corresponding close relationship to the daily diet), its recognizable signs of deficiency, and the generally short time period for developing symptoms of Vitamin K deficiency. Based on this analysis, Lipton draws two conclusions: (1) Symptoms of Vitamin K deficiency can be used to assess the potential effect of vegetable oil sterol esters on the uptake of Vitamin K; and (2) symptoms of Vitamin K deficiency are a sensitive indicator for potential effects of vegetable oil sterol esters on the uptake of all the fat-soluble vitamins. Following this analysis, Lipton evaluates published clinical studies conducted with plant sterols with a daily intake ranging from 3 grams to 25 grams and a duration ranging from 20 weeks to 260 weeks. Based on this evaluation, Lipton both concludes that the absence of reported clinical signs of Vitamin K deficiency is evidence that there was no notable effect on Vitamin K status in these studies and infers that the absence of effects on Vitamin K status is evidence that vegetable oil sterol esters will not have an effect on the uptake of fat-soluble vitamins other than Vitamin K.

Lipton describes a published uterotrophic assay and an unpublished two-generation reproduction study in rats. Based on these studies, Lipton concludes that vegetable oil sterol esters do not cause adverse reproductive effects. Lipton also describes a 13-week rat feeding study that has been discussed at an international scientific meeting. Based on this study, Lipton concludes that a dietary intake of approximately 3900 mg/kg bw/day did not result in any treatment-related effects in the rat. Lipton concludes that there is no need to investigate the potential carcinogenicity of vegetable oil sterol esters based on the lack of adverse effects (including pathology) in the 13-week rat feeding study; the lack of genotoxicity in unpublished genotoxicity studies; the minimal absorption and rapid elimination of phytosterols from the body; and the absence of structural alerts that would predict toxicity of vegetable oil sterol esters. Lipton's submission includes a letter from the National Toxicology Program (NTP), in which NTP has concluded, based in part on the results

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of data submitted by Lipton to NTP, that NTP will not proceed with its proposal to conduct multigeneration reproductive toxicity tests and chronic/carcinogenicity testing with β-sitosterol as a marker for saw palmetto.

FDA has evaluated the information in Lipton's submission as well as other available data and information, including the *Cytellin* file that is available at FDA's Center for Drug Evaluation and Research. In addition, FDA went to the office of Kleinfeld, Kaplan and Becker and evaluated certain data and information that were reviewed by Lipton's GRAS panel and by the NTP. Based on its evaluation, the agency has no questions at this time regarding Lipton's conclusion that vegetable oil sterol esters are GRAS under the intended conditions of use. Furthermore, FDA is not aware of any scientific evidence that vegetable oil sterol esters would be harmful. The agency has not, however, made its own determination regarding the GRAS status of the subject use of vegetable oil sterol esters. As always, it is Lipton's continuing responsibility to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

An evaluation that a use of a food ingredient is safe is a time-dependent judgment that is based on general scientific knowledge as well specific data and information about the ingredient. The intended use of vegetable oil sterol esters to help maintain healthy cholesterol levels as part of a diet low in saturated fat and cholesterol exemplifies a recent trend in the food industry to develop food ingredients that have a nontraditional function. The evolving scientific knowledge about such ingredients in the context of changing dietary patterns, including long-term nutritional implications, amplifies the time-dependent nature of any safety evaluation. Accordingly, the agency believes that it would be both prudent and responsible for Lipton to continue to monitor, through scientific studies or otherwise, consumers' dietary exposure to vegetable oil sterol esters and the long-term nutritional implications for individuals in all age groups who routinely consume the ingredient. In this regard, we were pleased to receive Lipton's letter dated April 28, 1999, which (1) describes initiatives that Lipton intends to have in place to ensure that its product is well understood by both consumers and health-care professionals and to encourage an ongoing exchange of information about the product once it is marketed; (2) describes ongoing clinical studies that are part of Lipton's continuing commitment to evaluate its product; and (3) states Lipton's commitment, as part of its ongoing discussion with FDA, to communicate with FDA as relevant information is developed from these initiatives and studies.

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Finally, we have been advised by the Office of Food Labeling (OFL) in the Center for Food Safety and Applied Nutrition that the proposed claim, "Helps promote healthy cholesterol levels as part of a diet low in saturated fat and cholesterol" falls within the purview of structure/function claims. However, as stated in OFL's letters of April 6, 1999, and April 20, 1999, the statement of identity for Take Control™ does not comply with the prominence requirements of 21 CFR 101.3(a) and 101.3(d). We would expect you to bring the statement of identity into compliance with the regulations. OFL is sending you a letter responding to the arguments in your April 20, 1999, letter discussing this issue. OFL has no other objection to your label.

Sincerely,

Alan M Rulis

Alan M. Rulis, Ph.D.
Director
Office of Premarket Approval
Center for Food Safety
and Applied Nutrition